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| EXAMINER | |
|---|---|
| RAO, MANJUNATH N | |
| ART UNIT | PAPER NUMBER |
| 1652 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/089,014 | NAKAYAMA ET AL. | |
| | Examiner | Art Unit | |
| | Manjunath N. Rao, Ph.D. | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 1-9 are currently pending and present for examination in this application.

### *Priority*

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

### *Drawings*

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 1-3 are directed to "A protein" or "DNA" with a specific enzyme/enzyme encoding activity which reads on the product of nature (for example, the enzyme/DNA of *Arabidopsis*). Amending the claims to recite "An isolated protein/ polynucleotide" to show the hand of man would overcome this rejection.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an enzyme with SEQ ID NO:1, encoded by a polynucleotide with SEQ ID NO:2 does not reasonably provide enablement for any such enzyme or its corresponding polynucleotide which is a derivative of the above enabled enzyme derived by deletion, substitution, addition or insertion of one or several amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-9 are so broad as to encompass any or all GDP-4-keto-6-deoxy-D-mannose-3,5-epimerase-4-reductase (ER) isolated from any or all sources including variants, mutants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of such enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to

which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single such enzyme. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides and polynucleotides with an undefined function/activity. The specification is limited to teaching the use of SEQ ID NO: 2, encoded by SEQ ID NO:1 as a ER but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any ER because the specification does not establish: (A) regions of the protein structure which may be modified without effecting its activity; (B) the general tolerance of said enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue on any such enzyme with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all ERs with an enormous number of amino acid modifications of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptide/polynucleotides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 is directed to polypeptide with SEQ ID NO:1 and variants of SEQ

ID NO:1. Claim 1 is rejected under this section of 35 USC 112 because the claim is directed to a genus of polypeptides derived from SEQ ID NO:1 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:1 and fragments of SEQ ID NO:1 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:1 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:1, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 2-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules with either SEQ ID NO:2 or DNA having the limitations of encoding a protein which is a variant of the polypeptide with SEQ ID NO:1.

The specification does not contain any disclosure of the structures of all DNA sequences that encode variants of SEQ ID NO:1. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonin et al. (Plant Physiol., Vol. 114(3), Sup. page 22, Abstract 20.). This rejection is based upon the public availability of a printed publication. Claims 1-3 of the instant application are drawn to a protein with SEQ ID NO:1 having a GDP-4-keto-6-deoxy-D-mannose-3, 5-epimerase-4-reductase activity or a variant thereof comprising an amino acid sequence derived from SEQ ID NO:1 wherein one or several amino acid residues are deleted, substituted, added or inserted and a polynucleotide encoding the same. Bonin et al. disclose a cDNA isolated from *A.thaliana* and encoding an identical polypeptide, and designated as *GER1* having GDP-4-keto-6-deoxy-D-mannose-3, 5-epimerase-4-reductase activity. While the above reference does not disclose the actual amino acid sequence or the polynucleotide sequence, Examiner takes the position that the amino acid sequence and the cDNA sequence of the reference enzyme is the same as the amino acid SEQ ID NO:1 or is a variant of SEQ ID NO:1 and the polynucleotide sequence SEQ ID NO:2 or is a variant of the same. Since there is no limitation placed on the number of changes that can be present in the polypeptide sequence, SEQ ID NO:1, for a variant polypeptide and its respective polynucleotide, claims 1-3 read on the cDNA and the encoded polypeptide disclosed by Bonin et al. Furthermore, as the source of the reference cDNA and the enzyme are the same as that of the claimed DNA and polypeptide Examiner also takes the position, that characteristics such as amino acid/nucleotide sequences are inherent characteristics. Thus Bonin et al. anticipate claims 1-3 of this application as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the

protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Claims 1-2, 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Andrianopoulos et al. (J. Bacteriol., Vol. 180(4):998-1001). This rejection is based upon the public availability of a printed publication. Claims 1-2, 4-8 of the instant application are drawn to a protein with SEQ ID NO:1 having a GDP-4-keto-6-deoxy-D-mannose-3, 5-epimerase-4-reductase activity or a variant thereof comprising an amino acid sequence derived from SEQ ID NO:1 wherein one or several amino acid residues are deleted, substituted, added or inserted and a polynucleotide encoding the same, an expression vector comprising the above polynucleotide, a transformant comprising the above expression vector and a process of producing the polypeptide by culturing the transformant and a transformant transformed with the vector above and a expression vector comprising the DNA encoding GDP-D-mannose-4,6-dehydratase (GMD) and a process for converting GDP-D-mannose into GDP-L-fucose using the above transformant. Andrianopoulos et al. disclose a cDNA encoding a protein having a GDP-4-keto-6-deoxy-D-mannose-3, 5-epimerase-4-reductase activity. Since there is no limitation placed on the number of changes that can be present in the polypeptide sequence, SEQ ID NO:1, for a variant polypeptide and its respective polynucleotide, Examiner considers the reference enzyme as a variant comprising an amino acid sequence derived from SEQ ID NO:1 wherein one or several amino acid residues are deleted, substituted, added or inserted. The reference also discloses the polynucleotide encoding the same, an expression vector comprising the above polynucleotide, a

transformant comprising the above expression vector and a process of producing the polypeptide by culturing the transformant and a transformant transformed with the vector above and a expression vector comprising the DNA encoding GDP-D-mannose-4,6-dehydratase (GMD) and a process for converting GDP-D-mannose into GDP-L-fucose using the cell extract of the above transformant. Therefore, Andrianopoulos et al. anticipate claims 1-2, 4-8 of this application as written.

***Conclusion***

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
June 12, 2003

MANJUNATH RAO
PATENT EXAMINER